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J. E. Greenleaf, Ames Research Center, Moffett Field, California

K. Simanonok and E. M. Bernauer, Human Performance Laboratory, University of California,  
Davis, California

C. E. Wade and L. C. Keil, Ames Research Center, Moffett Field, California

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**Ames Research Center**  
Moffett Field, California 94035-1000



# EFFECT OF HEMORRHAGE ON CARDIAC OUTPUT, VASOPRESSIN, ALDOSTERONE, AND DIURESIS DURING IMMERSION IN MEN

J. E. GREENLEAF, K. SIMANONOK,\* E. M. BERNAUER,\* C. E. WADE, AND L. C. KEIL

*NASA Ames Research Center*

## Summary

The purpose of this research was to test the hypothesis that a reduction in blood volume would attenuate or eliminate immersion-induced increases in cardiac output ( $\dot{Q}_{co}$ ) and urine excretion, and to investigate accompanying vasoactive and fluid-electrolyte hormonal responses. Eight men (19-23 yr) were supine during a 2-hr control period in air, and then sat for 5-hr test periods in air at 20°C (dry control, DC); water at 34.5°C (wet control, WC); and water (34.5°C) after hemorrhage (WH) of  $14.8 \pm 0.3\%$  of their blood volume. Blood volume was  $-11.6 \pm 0.6\%$  at immersion (time 0). Mean ( $\bar{X}$  hrs 1-5)  $\dot{Q}_{co}$  was unchanged in WC ( $5.3 \pm 0.01$  l/min) and in WH ( $4.5 \pm 0.1$  l/min), but decreased ( $P < 0.05$ ) in DC to  $3.6 \pm 0.1$  l/min. Mean urine excretion rates were  $1.0 \pm 0.2$  ml/min for DC and  $1.1 \pm 0.2$  ml/min for WH; both were lower ( $P < 0.05$ ) than that for WC of  $2.0 \pm 0.4$  ml/min. Plasma  $[Na^+]$  and  $[Osm]$  were unchanged in all experiments. Mean plasma vasopressin (PVP) ( $\bar{X}$  hrs 1-5) was  $1.1 \pm 0.1$  pg/ml in WC, and higher ( $P < 0.05$ ) in DC ( $2.1 \pm 0.2$  pg/ml) and WH ( $2.1 \pm 0.1$  pg/ml); it was unchanged during air and water test periods. Thus, hemorrhage attenuated the immersion-induced increase in  $\dot{Q}_{co}$ , eliminated the WC diuresis, maintained plasma renin activity and PVP at DC levels and did not change immersion-induced aldosterone suppression; the osmotic diuresis during control immersion is apparently not due to either aldosterone suppression or vasopressin suppression.

## Introduction

The increased excretion of water and electrolytes in humans during prolonged water immersion appears to be activated by the redistribution of body fluid into the thorax (refs. 5 and 8). This central hypervolemia, caused by fluid shifted from the legs and the lower torso (ref. 26) in conjunction with an absolute increase in plasma volume from an influx of interstitial fluid (refs. 11 and 21), stimu-

lates volume receptors within the capacitance vessels, the atria, and the pulmonary circuit. The sequence of events between receptor stimulation and diuresis is not well defined, but it is clear that interactions of plasma electrolytes, renin activity, and concentrations of aldosterone, vasopressin, and probably atriopeptin and urodilatin play significant roles in activating and sustaining the diuresis for control of fluid balance (refs. 4, 6, 9, and 19).

In normal subjects, a shift of about 700 ml of fluid (15% of the blood volume) into the upper thorax has been reported during immersion (ref. 1), but this volume shift has not been confirmed. If this fluid shift was attenuated or eliminated, then the diuresis should be attenuated or eliminated. A comparison of the differential cardiovascular and endocrine responses during immersion with normal diuresis, and diuresis attenuated by hemorrhage-induced hypovolemia, should provide additional insight into this mechanism. Therefore, the purpose of this study was to test the hypothesis that reduction, by hemorrhage, of the immersion-induced increase in central blood volume would attenuate the normal immersion-induced increases in cardiac output and urine flow.

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## Methods

### Subjects

Eight normal, healthy, male college students (19-23 yr) participated as test subjects (table 1). The study was conducted in the Laboratory for Gravitational Physiology-Immersion Facility at Ames Research Center. Each subject was fully informed of the procedures and risks, passed an extensive medical examination, and gave his written informed consent. The experimental protocol was approved by the human research committees at Ames and the University of California at Davis.

\*Human Performance Laboratory, University of California, Davis, CA 95616.

## Experimental Protocol

The subjects kept a daily log of their food and fluid intake, urine output, and physical activity, for the week prior to each of their three experiments: dry control (DC), wet control (WC), and wet hemorrhage (WH). They served as their own controls. The order of the DC and WC experiments was selectively randomized, but the WH experiment was conducted last. The three experiments were scheduled at weekly intervals and each subject was tested on the same day of the week. The subjects slept in the laboratory the night before each experiment; they were requested to satisfy their thirst and to drink an additional 500 ml of water just before retiring at about 2300 hr. No food or fluids were allowed between 2300 hr and the end of the experiment at 1400 hr the following day. On experiment day between 0630 and 0700 hr the subjects voided and were weighed (fig. 1); they did not shower. Each experiment began with the subject supine in air on an air mattress from 0700 to 0900 hr (hrs -2 to 0). During DC the mattress was on a table; during WC and WH the subjects floated on the mattress in the immersion tank to minimize exertion and possible syncopal responses when moving into the water. At 0900 hr they moved to the sitting position; in air ( $T_a = 20^\circ\text{C}$ ) during DC, and immersed to the neck in thermoneutral tap water ( $T_{H_2O} = 34.5 \pm 0.5^\circ\text{C}$ ) during WC and WH. Sixteen- or 18-gauge teflon catheters (Angiocath, Desert Medical, Sandy, Utah) were inserted into an antecubital vein before 0730 hr, and plasma volume was measured from 0750 to 0800 hr. The catheterized arm was supported horizontally in air in all experiments. The subjects stood briefly once each hour to urinate, and blood samples were taken hourly just after each voiding (fig. 1).

## Hemorrhage

In the wet hemorrhage experiment  $14.8 \pm \text{SE } 0.3\%$  of the blood volume was withdrawn as rapidly as possible (10-37 min) through a 16-gauge catheter beginning at hour -1 just after the 0800-hr urine collection (table 1, fig. 1). Three-way stopcocks (model K75, American Pharmaseal, Valencia, Calif.) were modified to accept a 2-m length of 3-mm i.d. Tygon tubing. This gas-sterilized assembly was flushed with 5 ml of 1000 Units/ml of heparin solution and then connected to the catheter to start the hemorrhage.

## Cardiovascular Measurements

Cardiac output ( $\dot{Q}_{CO}$ ) was measured hourly (hrs 0.5 to 4.5) with the  $\text{CO}_2$  rebreathing equilibration method (ref. 16), and  $\text{CO}_2$  concentrations were measured with a Beckman analyzer (model LB2, Brea, Calif.). No correction was made for changes in blood hemoglobin (Hb) concentration. Heart rate was measured with a Hewlett-Packard cardiometer modified with a battery for safety during immersion. Blood pressure was measured with a cuff and sphygmomanometer with the arm at heart level.

## Blood Sampling

Antecubital blood samples (10 ml each) were taken hourly without stasis through the 18-gauge indwelling catheter flushed with a  $\text{Na}^+$  heparin solution (0.33 U/ml). The samples were divided into three tubes; 2 ml into Venoject T-272Q tubes containing 3 mg dry EDTA for immediate red blood cell (RBC), Hb, and hematocrit (Hct) analyses;

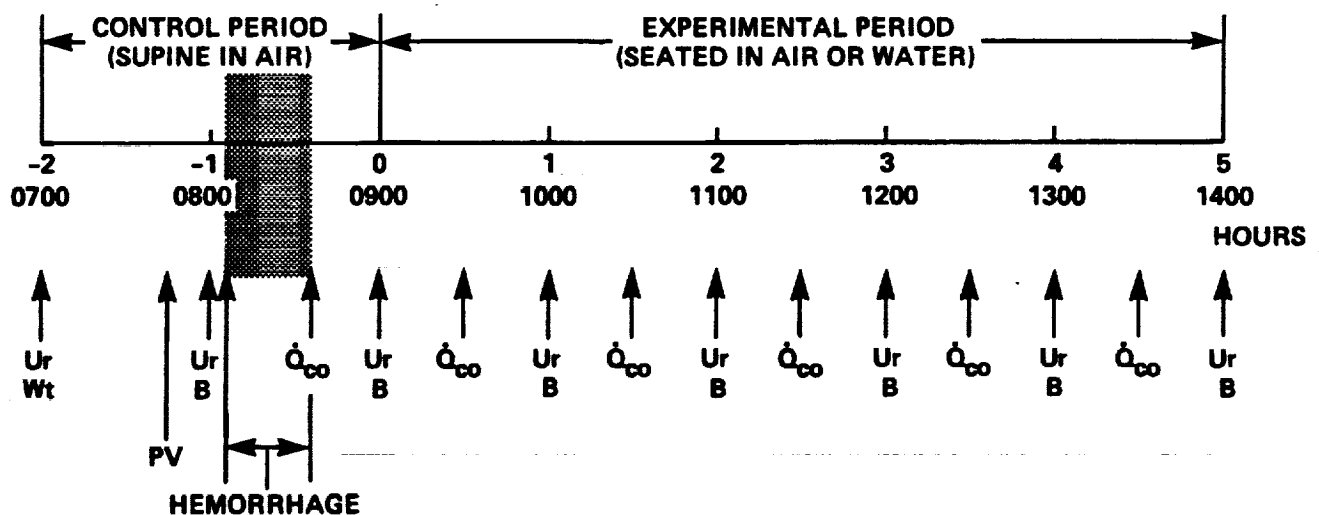


Figure 1. Experimental protocol with weight (Wt), plasma volume (PV), hemorrhage, cardiac output ( $\dot{Q}_{CO}$ ), urine (Ur), and blood (B) sampling times.

5 ml into Venoject T-206SQ tubes containing 7.5 mg dry EDTA for later analysis of plasma renin activity (PRA), vasopressin (PVP), aldosterone (PA), and cortisol; and 3 ml into Venoject T-273 SLH tubes containing 75 IU lithium heparin for later analysis of creatinine, glucose, osmolality, Na<sup>+</sup>, and K<sup>+</sup>. Plasma was frozen at -20°C. Excluding hemorrhage, 95 ml of blood were taken during each experiment and approximately 5 ml of T-1924 dye plus 15 ml of heparin solution were added, so the net fluid loss was about 75 ml.

### Urine and Blood Analyses

In plasma and urine the sodium and potassium concentrations were measured by flame photometry (model 643, Instrumentation Laboratory, Inc., Lexington, Mass.), and osmolality by freezing point depression (Advanced Digimatic Osmometer model 30II, Needham Heights, Mass.). Creatinine concentrations were determined with a rate-dependent modification of the Jaffe reaction (ref. 24). Plasma total protein concentration was measured with an optical refractometer (National, Baltimore, Maryland) and plasma glucose concentration was measured spectrophotometrically (Beckman Instruments, Brea, Calif.).

Plasma vasopressin (ref. 17) and renin activity (Angiotensin I kit, New England Nuclear, North Billerica, Mass.) were measured with sensitivities of 0.3 pg/ml and 2 ng Ang I/ml/hr, respectively; cortisol (Rainen kit, New England Nuclear, North Billerica, Mass.), and aldosterone (Coat-A-Count kit, Diagnostics Products Corp., Los Angeles, Calif.) were measured by radioimmunoassay. Intra- and inter-assay variabilities were: PVP 9% and 12%, PRA 8.7% and 10%, cortisol 2.5% and 5%, and PA 5.1% and 7.1%, respectively.

Hematocrit was measured four times using heparinized microhematocrit tube (Monoject Scientific, St. Louis, Missouri) spun for 5 min at 11,500 rpm in an International Equipment Co. centrifuge (model MB, Needham Heights, Mass.) and read on a modified International (model CR) microcapillary reader within  $\pm 0.2$  units. Hemoglobin was measured in quadruplicate to  $\pm 0.1$  g/dl with the cyanomethemoglobin method (Coulter Electronics, Hialeah, Florida). Plasma volume (PV) was measured from one 10-min post-injection blood sample (ref. 10), using Evan's Blue Dye - T1824 (Harvey Laboratories, Inc., Philadelphia, Penn.) with a method modified from Campbell et al. (refs. 3 and 10). Intersubject variability was  $\pm 25$  ml (ref. 10). Plasma volume was measured prior to the first experiment. The dye was injected before each experiment but it was measured once before the test period began (PV<sub>b</sub>), but only in the DC and WC experiments. Mean ( $\pm$ SE) PV before the control, DC and WC experiments were  $3,390 \pm 127$  ml,  $3,577 \pm 149$  ml, and

$3,484 \pm 145$  ml, respectively. Change in PV was calculated with Hb-Hct transformation equation (ref. 10) from time 0, after hemorrhage was completed, so values from the three experiments would be comparable. The initial (hr -1) blood volume (BV<sub>b</sub>) was calculated from the measured PV<sub>b</sub>:

$$BV_b = PV_b \frac{100}{100 - (Hct_b \times 10^{-2})(0.96)(0.91)} \quad (1)$$

where:

b = before blood sampling or hemorrhage

0.96 is the Hct correction for trapped plasma

0.91 is the correction of F-cell ration of whole-body Hct to peripheral large-vessel Hct (ref. 14).

Subsequent blood volume values during immersion (BV<sub>a</sub>) were calculated from the red cell mass (RCM) and hematocrit (eq. (9)).

$$BV_a = PV_a + RCM_a \quad (2)$$

$$PV_a = V_b - PV_s + TCF \quad (3)$$

$$RCM_a = RCM_b - RCM_s \quad (4)$$

Therefore,

$$BV_a = (PV_b - PV_s + TCF) + (RCM_b - RCM_s) \quad (5)$$

The hematocrit of the blood sample or hemorrhage volume is defined by

$$Hct_s = RCM_s / (PV_s + RCM_s) \quad (6)$$

Substituting from equations (3) and (4),

$$Hct_a = \frac{(RCM_b) - (RCM_s)}{(PV_b - PV_s + TCF) + (RCM_b - RCM_s)} \quad (7)$$

Rearranging,

$$TCF = \frac{RCM_b - RCM_s}{Hct_a} - PB_b + PV_s - RCM_b + RCM_s \quad (8)$$

Substituting equation (8) into equation (5),

$$BV_a = \frac{RCM_b - RCM_s}{Hct_a} \quad (9)$$

where

a = after blood sampling or hemorrhage

b = before blood sampling or hemorrhage

s = blood sampling or hemorrhage

BV = blood volume, ml

PV = plasma volume, ml

=  $BV[1 - (Hct \times 10^{-2})(0.96)(0.91)]$

$PV_s$  = PV lost by sampling or hemorrhage, ml  
 $= BV_s[1 - (Hct_s \times 10^{-2}) (0.96)]$   
 $RCM_b$  = red cell mass, ml  
 $= BV_b (Hct_b \times 10^{-2}) (0.96) (0.91)$   
 $RCM_s$  = RCM lost by sampling or hemorrhage, ml  
 $= BV_s (Hct_s \times 10^{-2}) (0.96)$   
 $Hct_s$  = hematocrit of blood sample or hemorrhage volume  
 $TCF$  = transcapillary flux, ml (positive when circulatory refill occurs)

The assumptions for these calculations were that the number of red blood cells was constant, that 0.91 was a proper F-cell ratio during immersion, and that the mean corpuscular volume (MCV) did not change. The latter is defined as

$$MCV(\mu^3) = 10(Hct \times 10^{-2}) (0.96)/[RBC] \times 10^6 \cdot mm^{-3} \quad (10)$$

### Statistical Analyses

The Wilcoxon signed-rank test and the dependent t-test were used; linear correlation coefficients were calculated. Analyses of the hemorrhage experiment data were performed between hr -1 data and subsequent immersion values, rather than using the mean of hr -1 and hr 0 values as in the two control experiments. Mean data over the 5-hr test periods designated ( $\bar{X}$  1-5 hr), were also compared using ANOVA. The null hypothesis was rejected when  $P < 0.05$ , and nonsignificant differences were denoted by NS.

## Results

### Blood Volume and Transcapillary Flux

The blood volume was influenced by hourly blood sampling, hemorrhage, urine, and respiratory losses, and transvascular fluid shifts. The effects of urine and respiratory water losses were accounted for by changes in the Hct. One hr before immersion in the WH experiment,  $838 \pm 38$  ml ( $14.8 \pm 0.3\%$ ) of blood (range 734 to 1,053 ml) were withdrawn in 10 to 37 min (table 1). However, interstitial to vascular fluid flux ( $\bar{X} = 170 \pm 29$  ml), which occurred during hemorrhage and before immersion (hr 0), reduced the hypovolemia at the moment of immersion to 668 ml, about  $11.6 \pm 0.6\%$  ( $P < 0.05$ ) of the original blood volume (table 1, fig. 2). The changes in BV

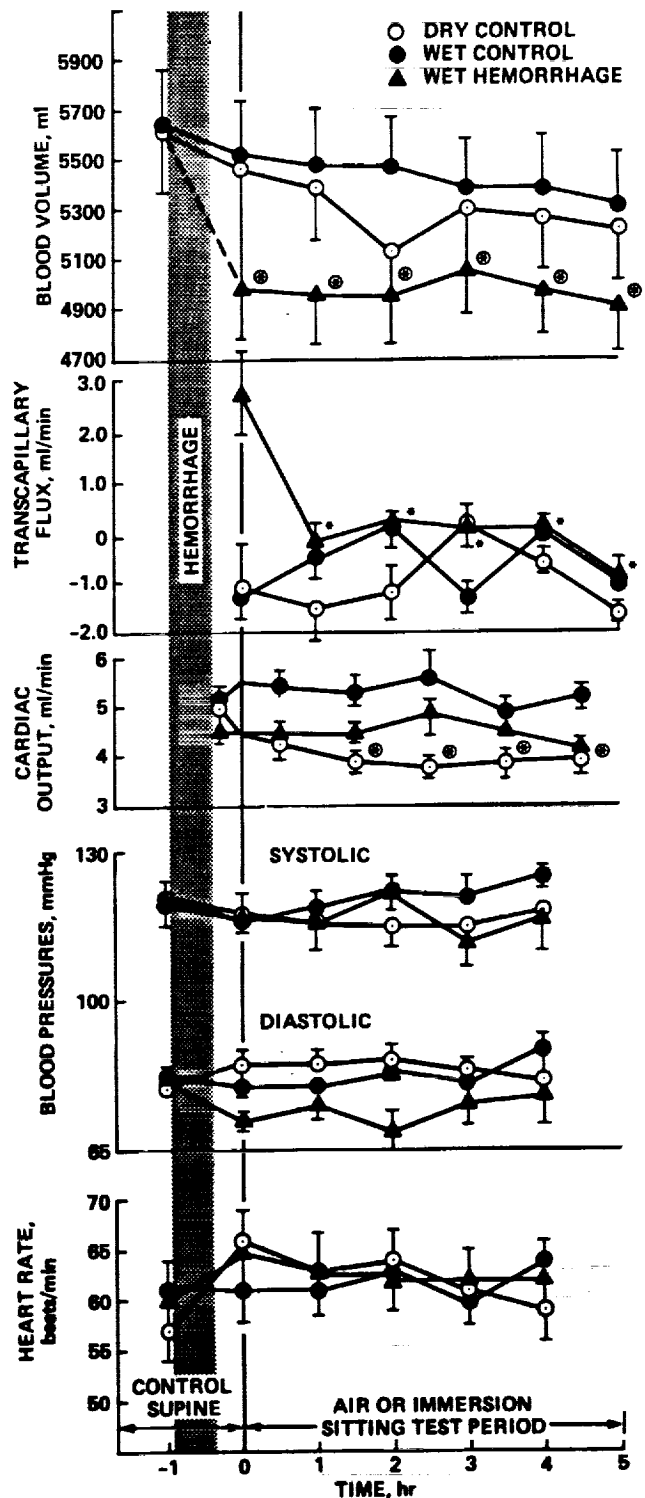


Figure 2. Mean ( $\pm$ SE) blood volume, transcapillary flux, cardiac output, blood pressures, and heart rate during the three experiments. \* $P < 0.05$  from mean control value (mean of hr -1 and hr 0 values); \* $P < 0.05$  from control value (hr -1 value).



from hr -1 to hr 0 in the DC and WC experiments were not significantly different. During the 5-hr sitting test periods, BV exhibited decreasing trends (NS) in the two control experiments, but the reduced BV in the WH experiment remained essentially constant (fig. 2).

Mean ( $\pm$ SE) calculated transcapillary fluxes throughout immersion ( $\bar{X}$  1-5 hr) were negative (vascular to interstitial direction) during all three experiments (fig. 2): for DC  $-0.61 \pm 0.13$  ml/min ( $183 \pm 38$  ml total volume) for WC  $-0.52 \pm 0.10$  ml/min ( $156 \pm 31$  ml) (NS from the DC value), and for WH  $-0.09 \pm 0.07$  ml/min ( $27 \pm 20$  ml) which was significantly higher ( $P < 0.05$ ) than both the DC and WC values.

### Cardiovascular Responses

Both systolic (SBP) and diastolic (DBP) blood pressures were essentially unchanged during the sitting test periods in the three experiments (fig. 2). Mean  $\pm$  SE ( $\bar{X}$  hrs 1-5) SBP were  $116 \pm 3$  mm Hg for DC,  $122 \pm 2$  mmHg for WC (NS), and  $116 \pm 4$  mmHg for WH ( $P < 0.05$  from WC). Mean DBP were  $81 \pm 2$  mmHg for DC,  $81 \pm 2$  mmHg for WC (NS), and  $75 \pm 4$  mmHg for WH ( $P < 0.05$  from WC and DC). Mean  $\pm$  SE heart rates were  $62-63 \pm 2-3$  beats/min for the three experiments (all NS).

Cardiac output over hrs 0.5 to 4.5 was unchanged during WC and WH, but was depressed ( $P < 0.05$ ) from the -0.5 hr control level at hrs 1.5 to 4.5 in DC (fig. 2). The mean ( $\bar{X}$  hrs 1.5 to 4.5) cardiac output for DC ( $3.6 \pm 0.1$  l/min) was lower by 33% than the mean from WC of  $5.3 \pm 0.1$  l/min, and lower by 21% than the mean for WH of  $4.5 \pm 0.1$  l/min; the values for WC and WH were different ( $P < 0.05$ ) from each other. These mean differences in cardiac outputs during the sitting test periods were primarily due to changes in stroke volume, because the mean heart rates did not differ among the three groups (fig. 2).

### Renal Responses

During the supine control periods urinary excretion rate increased only in DC, from  $0.8 \pm 0.3$  to  $1.8 \pm 0.5$  ml/min ( $P < 0.05$ ) (fig. 3). During the 5-hr sitting test periods excretion decreased to an equilibrium level of  $0.6 \pm 0.1$  ml/min ( $P < 0.05$ ) in DC; increased progressively from  $0.8 \pm 0.2$  ml/min (hr -1) to 1.2-1.3 ml/min ( $P < 0.05$ ) at hrs 3-4 in WH; and, in WC, exhibited the characteristic large increase from a mean supine control level (hrs -1 and 0) of  $1.1 \pm 0.3$  ml/min to  $3.3 \pm 0.9$  ml/min ( $P < 0.05$ ) at hr 1, declining progressively thereafter. The mean ( $\bar{X}$  hrs 1-5) urine excretion rates during DC and WH were  $1.0 \pm 0.2$  and  $1.1 \pm 0.2$  ml/min (NS), respectively; both

were significantly lower ( $P < 0.05$ ) than the mean rate of  $2.0 \pm 0.4$  ml/min during WC (fig. 3). Thus, prior hemorrhage significantly attenuated the normal immersion diuresis to a rate essentially equal to that in the DC experiment.

The urinary osmotic clearance responses followed the osmolar excretion (table 2) and urinary excretion (fig. 3) responses; the values for DC were significantly lower than those for both WH and WC, and the WC values were higher ( $P < 0.05$ ) than those for WH. Urinary  $\text{Na}^+$  and  $\text{K}^+$

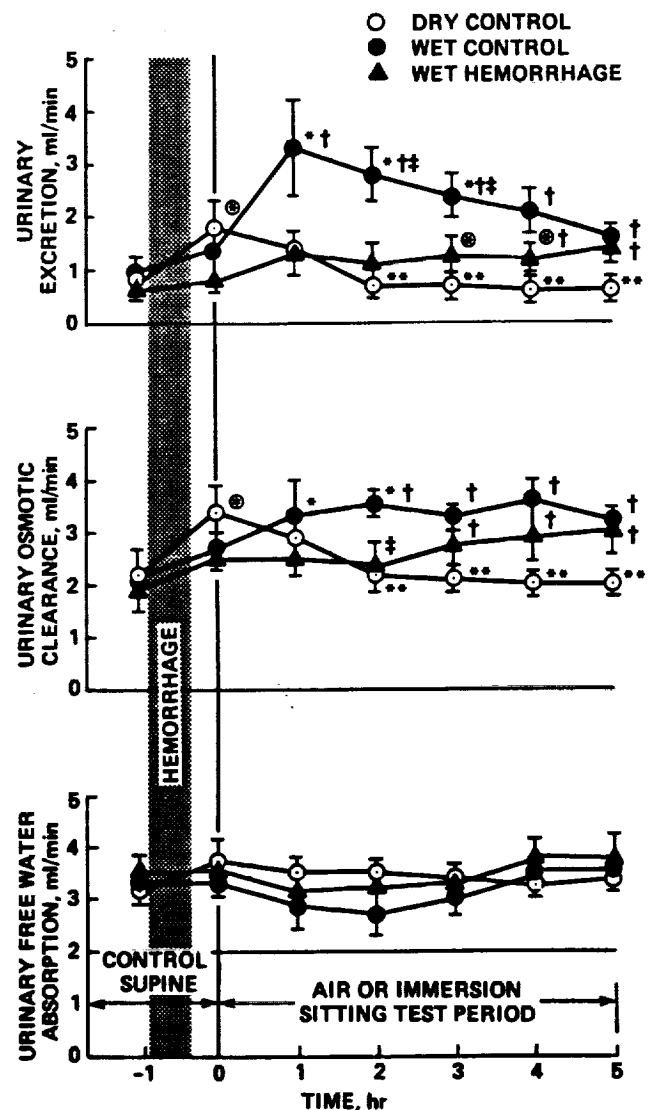


Figure 3. Mean ( $\pm$ SE) urinary excretion, urinary osmotic clearance, and urinary free water absorption during the three experiments. \* $P < 0.05$  from mean control value (mean of hr -1 and hr 0 values); † $P < 0.05$  from control value (hr -1 value); ‡ $P < 0.05$  from corresponding DC value; †† $P < 0.05$  from corresponding WC value; \*\* $P < 0.05$  from hr 0 value.

clearances also were similar to urinary excretion rates (table 2). There were no significant changes in urinary free water absorption within or between the three experiments; the mean ( $\bar{X}$  hrs 1-5) values were  $1.4 \pm 0.1$  ml/min for DC,  $1.1 \pm 0.2$  ml/min for WC, and  $1.4 \pm 0.1$  ml/min for WH. Thus, the WC diuresis was mainly osmotic throughout immersion, while the diuresis during wet hemorrhage tended to become more osmotic as immersion progressed (fig. 3).

Creatinine clearance did not change during any of the sitting test periods, but the mean ( $\bar{X}$  hrs 1-5) rates for WC ( $170 \pm 6$  ml/min) and WH ( $157 \pm 8$  ml/min) were both higher ( $P < 0.05$ ) than those for DC ( $131 \pm 7$  ml/min) (table 2).

### Blood Responses

Plasma volume (calculated) decreased immediately to a mean level of  $-3.3 \pm 0.2\%$  ( $P < 0.05$ ) during the DC sitting test period (fig. 4). During WC, after a 2-hr delay, the plasma volume changed from  $-2.6 \pm 0.7\%$  at hr 3 to  $4.9 \pm 0.9\%$  (both  $P < 0.05$ ) at hr 5. However, WH plasma volume was unchanged and it remained higher ( $P < 0.05$ ) than both DC and WC levels during hrs 3-5.

Plasma Hb, Hct, total protein, and RBC concentrations responded inversely to the plasma volume changes, with significantly increasing levels during the two control experiments and significantly lower and remarkably constant levels in WH (figs. 4 and 5). The initial (0 to 1 hr) decreased WH response reflected the large -1 to 0-hr interstitial-to-vascular transcapillary fluid flux (fig. 2) that increased blood vol. from  $-14.8\%$  to  $-11.6\%$ . Average-mean corpuscular volumes did not change during the sitting test periods or differ among experiments; the values ( $\bar{X}$  hrs 1-5) were  $88.0 \pm 0.3 \mu^3$  for DC,  $88.0 \pm 0.0 \mu^3$  for WC, and  $87.2 \pm 0.6 \mu^3$  for WH.

With one exception, plasma  $\text{Na}^+$ ,  $\text{K}^+$ , and osmotic concentrations were unchanged during the sitting test period in all three experiments (fig. 6); and mean ( $\bar{X}$  hrs 1-5) values were not different among experiments. The exception was the elevated ( $P < 0.05$ ) wet control  $\text{K}^+$  at hr 1.

Plasma aldosterone concentrations were not different during the three supine control periods. The concentrations decreased by 4-5 ng/dl ( $P < 0.05$ ) from hr -1 to hr 0 in all three experiments, and continued to decrease in the WC and WH sitting test periods to reach about 7 ng/dl (fig. 6). Aldosterone remained at the time 0 control level of 12-14 ng/dl in the final 3 hr of DC.

Mean plasma creatinine concentrations (i.e., GFR) did not change during the sitting test periods or differ among experiments; the values were  $0.1 \pm 0.01$  mg/dl for DC,

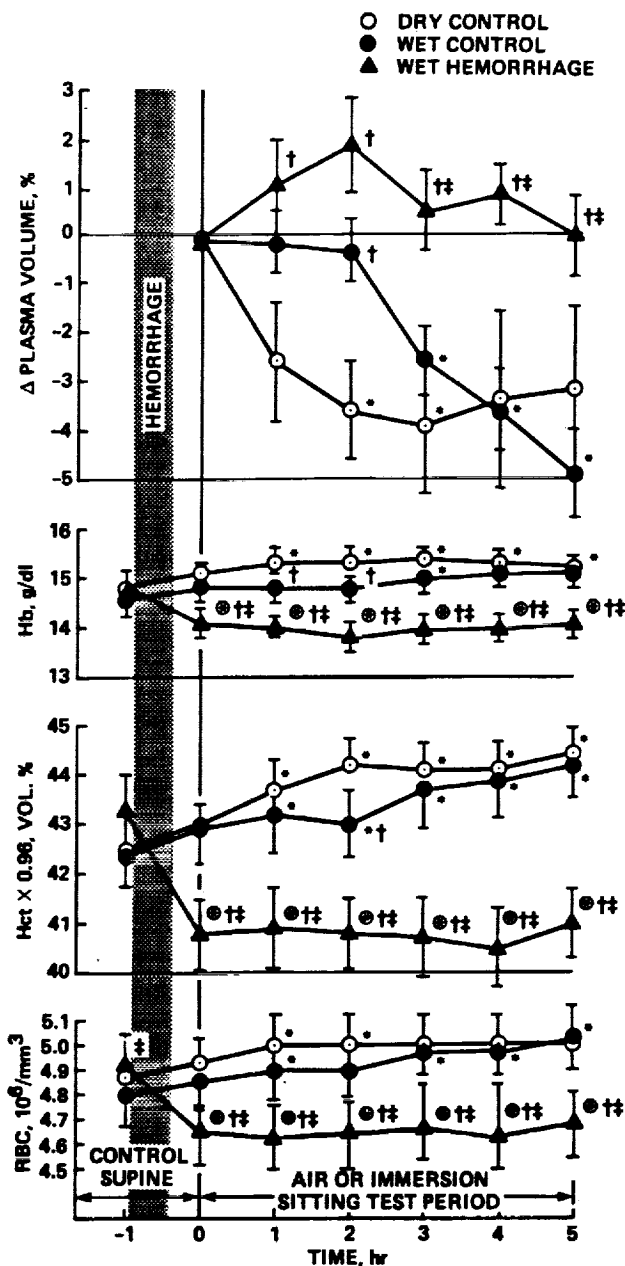


Figure 4. Mean ( $\pm$ SE) change in plasma volume, hemoglobin (Hb), hematocrit (Hct), and red blood cell (RBC) concentrations during the three experiments. \* $P < 0.05$  from mean control value (mean of hr -1 and hr 0 values);  $^{\circ}P < 0.05$  from control value (hr -1 value);  $^{\dagger}P < 0.05$  from corresponding DC value;  $^{\ddagger}P < 0.05$  from corresponding WC value.

$0.1 \pm 0.01$  mg/dl for WC, and  $0.1 \pm 0.01$  mg/dl for WH. The plasma glucose concentration increased from  $82 \pm 3$  to  $87 \pm 3$  mg/dl ( $P < 0.05$ ) after hemorrhage and remained essentially constant; it was not significantly different from glucose concentrations in the two control experiments

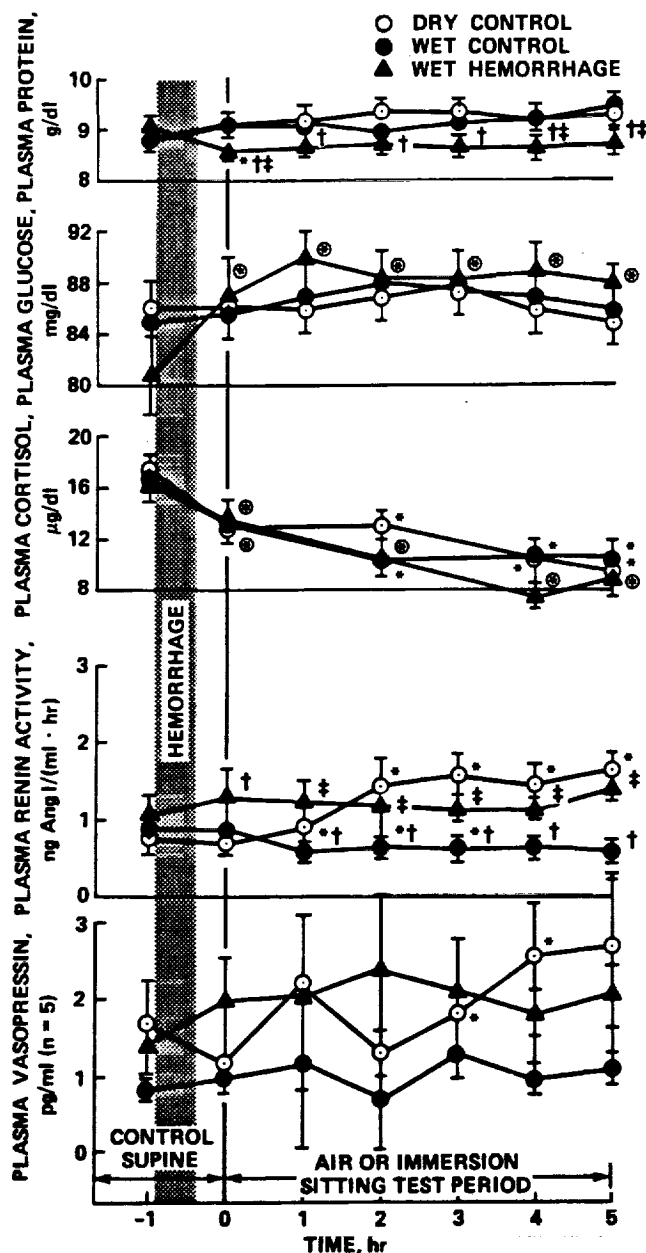


Figure 5. Mean ( $\pm$ SE) plasma protein, glucose, cortisol, renin activity, and vasopressin concentrations during the three experiments. \* $P < 0.05$  from mean control value (mean of hr -1 and hr 0 values);  $^{\circ}P < 0.05$  from control value (hr -1 value);  $^{\dagger}P < 0.05$  from corresponding DC value;  $^{\ddagger}P < 0.05$  from corresponding WC value.

during the sitting test periods (fig. 5). Despite hemorrhage and vascular refill, plasma cortisol concentration decreased from a control level of about 16  $\mu$ g/dl to about 10  $\mu$ g/dl ( $P < 0.05$ ) at hr 5 in all experiments; there was no significant difference between the three experiments during the sitting test period (fig. 5).

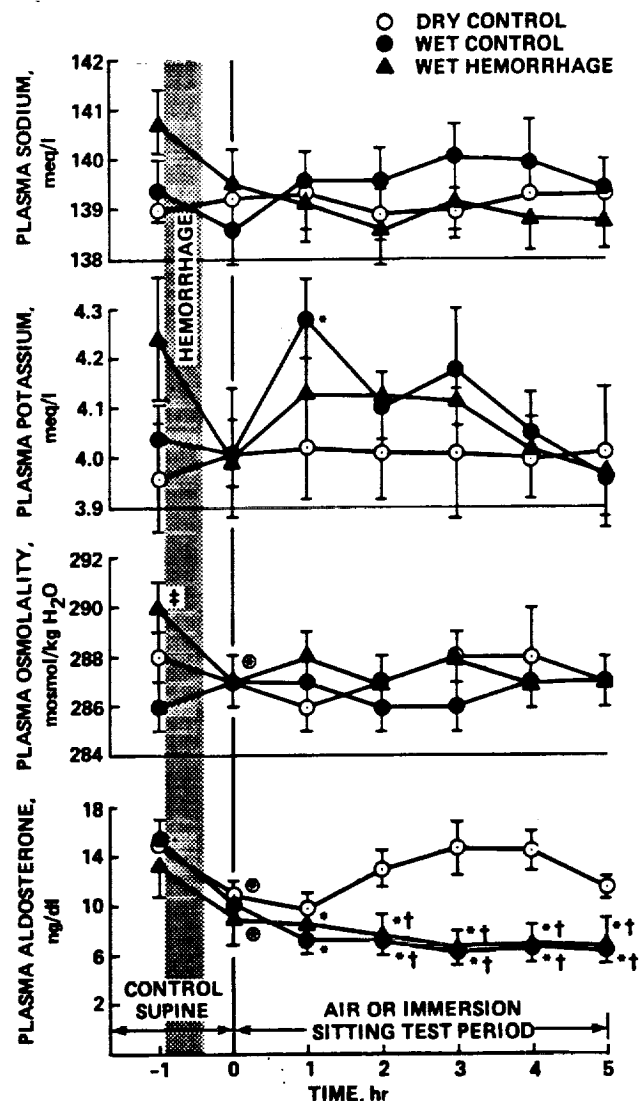


Figure 6. Mean ( $\pm$ SE) plasma sodium, potassium, osmolality, and aldosterone concentrations during the three experiments. \* $P < 0.05$  from mean control value (mean of hr -1 and hr 0 values);  $^{\circ}P < 0.05$  from control value (hr -1 value);  $^{\dagger}P < 0.05$  from corresponding DC value;  $^{\ddagger}P < 0.05$  from corresponding WC value.

Plasma renin activity was not changed significantly by hemorrhage. It increased ( $P < 0.05$ ) during the DC sitting test period and decreased ( $P < 0.05$ ) slightly during the WC test period. The mean ( $\bar{X}$  hrs 1-5) level for WC ( $0.57 \pm 0.01$  ng AngI/ml  $\times$  hr) was lower ( $P < 0.05$ ) than those for DC ( $1.43 \pm 0.13$  ng AngI/ml  $\times$  hr) and WH ( $1.26 \pm 0.05$  ng AngI/ml  $\times$  hr); the latter two levels were not different from each other (fig. 5).

Hemorrhage did not change the control plasma vasopressin concentration (hr -1 vs. hr 0), but the mean

( $\bar{X}$  hrs 1-5) PVP level for WH was higher ( $P < 0.05$ ) than the hr -1 value (fig. 5). Plasma vasopressin concentrations during the sitting test periods increased significantly from the control (hr -1 and hr 0) level only in DC, at hr 3 and 4. Like the PRA responses, the mean ( $\bar{X}$  hrs 1-5) PVP level for WC ( $1.1 \pm 0.1$  pg/ml) was lower ( $P < 0.05$ ) than those for DC ( $2.1 \pm 0.2$  pg/ml) and WH ( $2.1 \pm 0.1$  pg/ml); the latter two levels were not different from each other (fig. 5). These different PVP levels were associated with similar and unchanged levels of urinary free water absorption (fig. 3).

## Discussion

The most important finding was that the effective hemorrhage-induced hypovolemia ( $-11.8 \pm 0.7\%$ ) before immersion removed the stimulus for the normal increase in cardiac output and diuresis. The net loss of fluid (after transvascular flux) was about 668 ml. This loss was similar to the increase in central blood volume during immersion of about 700 ml (ref. 1) calculated from blood mean transit time through the lungs and cardiac output (1). The origin of this shifted blood volume has been ascribed to the lower limbs and lower thorax (ref. 26), but Tajima et al. (ref. 26) studied head-out immersion-induced fluid translocation in normal and in legless men and found that the latter had the same three-fold increase in urinary excretion as the normal men. Arm fluid translocation was minimal. Thus, fluid shift from only the lower torso appears to be sufficient to instigate "normal" immersion-induced diuresis.

For the sitting test periods, the WH urinary excretion rate was not significantly different from that during the DC experiment, while the WC excretion increased to the usual level (3.2-3.5 ml/min) when fluid was not ingested during immersion (ref. 18). Therefore, assumption of the supine position for 1 hr prior to immersion, which was necessary to prevent fainting during hemorrhage, did not appear to alter the WC diuresis. But urinary excretion and osmotic clearance tended to increase, while plasma aldosterone decreased, in all three experiments in the supine control period. These accentuated supine control responses probably attenuated some subsequent responses during immersion.

Urinary excretion rates during the sitting test periods followed the cardiac output responses; WC values were highest, WH values were intermediate, and DC values were lowest. Since heart rates did not change throughout the three experiments, changes in cardiac output were due to changes in stroke volumes from, presumably, the headward fluid shifts. Neither systolic nor diastolic blood pressure changed in the three experiments, but diastolic

pressure in the WH experiment tended to be lower throughout immersion, suggesting a slightly reduced pressure with hypovolemia.

The sustained 33% increase in cardiac output (WC vs. DC) agrees with the 32% increase reported by Arborelius et al. (ref. 1), who also compared immersion data with air data using the dye-dilution technique. They also observed no change in heart rate with immersion. Farhi and Linnarsson (ref. 7) reported that cardiac output in air, calculated from the rate of rise of  $\text{CO}_2$  at the mouth, started at  $5.1 \pm 0.09$  l/min and rose to  $8.3 \pm 0.09$  l/min ( $\Delta = +39\%$ ). This is in agreement with the findings reported above (refs. 1 and 7) and with Begin et al. (ref. 2), who found a sustained increase in pulmonary capillary blood flow of 20 to 40% during 4 hr of head-out immersion. The WH cardiac output was unchanged during immersion, presumably due to the hemorrhage-induced hypovolemia.

Also, plasma volume did not change during the sitting test period after hemorrhage, partly because of unchanged transcapillary influx; however, plasma volume was reduced significantly in the two control experiments. The constant plasma volume in WC during the first 2 hr of immersion was probably due to the absolute increase in plasma volume of 6-8% (not measured) during the first 30 min (refs. 11 and 21). Plasma volume continued to decrease linearly in the WC experiment after hr 2; it reached equilibrium in the DC experiment at hr 3. Thus, a portion of the WC plasma volume response was caused by the change from the control supine to the immersion sitting posture. The 2-hr supine control period probably allowed some "hypervolemia" to occur, so there was a greater percentage reduction in plasma volume during the two control experiments than would have occurred if the subjects had been sitting during the control period.

The slowly decreasing plasma cortisol concentrations associated with the normal circadian rhythm, coupled with the constant heart rates and blood pressures during the three sitting test periods, indicated no untoward "stress" from the hemorrhage.

Increases in glomerular filtration rates (estimated from creatinine clearances) could not account for the elevated urinary volume in WC and the similar volumes in DC and WH, because creatinine clearances were elevated significantly in both WC and WH above those in DC. Yet some data on dogs suggest that activating cardiac stretch receptors during immersion causes natriuresis by reflex suppression of renal sympathetic nerve activity, independently of changes in GFR. Miki et al. (ref. 20) found that renal sympathetic nerve activity was reduced by about 50% during immersion in dogs, and renal denervation abolished the natriuresis and diuresis. But this may not be

a primary mechanism causing natriuresis and diuresis in humans, because paraplegic men with cervical lesions at C5-C8 exhibit essentially normal immersion urinary diuresis (ref. 26).

In the DC experiment the decreasing urinary osmotic clearance and sodium excretion during the sitting test period could have been caused by the increasing plasma aldosterone concentrations. However, the correlation coefficient between plasma aldosterone and urinary osmotic clearance during the test period was only 0.22 (NS). Since free water absorption did not change significantly within or between the three experiments, it is clear that the WC diuresis was mainly osmotic, while the WH urinary excretion rate was similar to DC for the first 2 hr of immersion and tended to increase thereafter. This increasing excretion rate in WH was accompanied by increasing osmotic clearance. Urine  $\text{Na}^+$  and osmotic excretions were significantly greater in the two immersion experiments than in the DC experiment. The accompanying significant reductions in plasma aldosterone concentrations during immersion is suggested as a contributory mechanism for the  $\text{Na}^+$  loss and osmotic diuresis. The low nonsignificant correlation coefficients between plasma aldosterone and renin activity for DC, WC, and WH of 0.11, 0.08, and 0.03, respectively, indicated a dissociation between these two variables that was not influenced by prior hemorrhage.

Plasma vasopressin did not change significantly during any sitting test period, but the mean ( $\bar{X}$  hrs 1-5) values for WC were significantly lower by about 1.0 pg/ml than those for DC and WH, which tended to increase slightly during their respective test periods. The overnight food and fluid restriction did not elevate PVP significantly. Only one subject in each of the three experiments had lower hr -1 PVP compared with his hr -0 level; these PVP values (for hr 0 and 1, respectively) were 1.2 and 0.7 pg/ml for DC, 0.6 and 0.2 pg/ml for WC, and 2.0 and 0.8 pg/ml for WH. Even though systemic blood pressures were unchanged in all experiments during the test periods, the highest cardiac outputs and presumably central venous pressures (in WC) were associated with the lowest levels of PVP. The correlation coefficient ( $r$ ) between cardiac output and PVP was +0.25 ( $N = 5$ ,  $df = 73$ ,  $P < 0.05$ ), indicating no negative relationship between these two variables. The correlation coefficient changed somewhat to +0.33 ( $N = 5$ ,  $df = 23$ , NS) when data only from WC were analyzed.

Norsk et al. (ref. 22) found a correlation coefficient of only -0.39 ( $N = 183$ ,  $P < 0.001$ ) between central venous pressure and PVP measured in immersed subjects after infusion of 3000 ml of isotonic saline and withdrawal of 500 ml of blood. This coefficient indicates that only 15%

( $r^2$ ) of the variance in PVP could be accounted for by changes in central venous pressure under their conditions. Also, Shiraki et al. (ref. 25) have reported a dissociation between immersion-induced PVP and diuresis, especially during immersion at night when PVP was depressed and diuresis was unchanged from control levels. There has been a sufficient number of studies in which plasma vasopressin has remained unchanged during significant immersion-induced diuresis in normally hydrated subjects (refs. 11-13, 15, 18, 23, and 25) to question whether PVP suppression is a major mechanism for the instigation and maintenance of this diuresis.

In summary, the immersed subjects maintained normal ambulatory cardiac output and urinary excretion rate when their effective blood volume was depleted by 11.6%; i.e., the hypovolemia attenuated of the usual immersion-induced increases in cardiac output and urinary output. Hemorrhaged immersed subjects also maintained PRA and PVP levels unchanged at their dry-control levels, but their immersion-induced aldosterone suppression was similar in both immersion experiments. Thus, the osmotic diuresis in the wet control experiment could be explained by the suppression of aldosterone, but aldosterone was also suppressed with no diuresis during the wet hemorrhage experiment. Factors other than PVP and aldosterone suppression must be involved in the control of fluid volume during immersion.

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13. ABSTRACT (Maximum 200 words)  The purpose of this research was to test the hypothesis that a reduction in blood volume would attenuate or eliminate immersion-induced increases in cardiac output ( $\dot{Q}_{co}$ ) and urine excretion, and to investigate accompanying vasoactive and fluid-electrolyte hormonal responses. Eight men (19-23 yr) were supine during a 2-hr control period in air, and then sat for 5-hr test periods in air at 20°C (dry control, DC); water at 34.5°C (wet control, WC); and water (34.5°C) after hemorrhage (WH) of $14.8 \pm 0.3\%$ of their blood volume. Blood volume was $-11.6 \pm 0.6\%$ at immersion (time 0). Mean ( $\bar{X}$ hrs 1-5) $\dot{Q}_{co}$ was unchanged in WC ( $5.3 \pm 0.01$ l/min) and in WH ( $4.5 \pm 0.1$ l/min), but decreased ( $P < 0.05$ ) in DC to $3.6 \pm 0.1$ l/min. Mean urine excretion rates were $1.0 \pm 0.2$ ml/min for DC and $1.1 \pm 0.2$ ml/min for WH; both were lower ( $P < 0.05$ ) than that for WC of $2.0 \pm 0.4$ ml/min. Plasma $[Na^+]$ and $[Osm]$ were unchanged in all experiments. Mean plasma vasopressin (PVP) ( $\bar{X}$ hrs 1-5) was $1.1 \pm 0.1$ pg/ml in WC, and higher ( $P < 0.05$ ) in DC ( $2.1 \pm 0.2$ pg/ml) and WH ( $2.1 \pm 0.1$ pg/ml); it was unchanged during air and water test periods. Thus, hemorrhage attenuated the immersion-induced increase in $\dot{Q}_{co}$ , eliminated the WC diuresis, maintained plasma renin activity and PVP at DC levels and did not change immersion-induced aldosterone suppression; the osmotic diuresis during control immersion is apparently not due to either aldosterone suppression or vasopressin suppression.				
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